(FILE 'HOME' ENTERED AT 15:31:52 ON 19 MAY 2004)

FILE 'CAPLUS' ENTERED AT 15:32:01 ON 19 MAY 2004
L1 1 S (PROTEIN DESIGN) AND (ACTIVE DOMAIN)
L2 160 S (PROTEIN DESIGN) AND (DOMAIN)
L3 1 S (PROTEIN DESIGN) AND (ACTIVE (3W)DOMAIN)
L4 1 S (PROTEIN DESIGN) AND (INSERT? (3W)DOMAIN)
L5 0 S (PROTEIN (5A) (DE NOVO)) AND (INSERT? (3W)DOMAIN)
L6 186 S (PROTEIN (5A) (DE NOVO)) AND (DOMAIN)
L7 334 S L2 OR L6

=> d bib,abs 256,261,263,266,268,269,277,279,282,296,299,302,305,308

L7 ANSWER 256 OF 334 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:300280 CAPLUS
DN 124:335761
TI Boehringer Mannheim Award Lecture 1995/La conference Boehringer Mannheim 1995. **De novo** design of α-helical **proteins**: basic research to medical applications
AU Hodges, Robert S.
CS Dep. Biochem. Protein Eng. Network Cent. Excellenece, Univ. Alberta, Edmonton, AB, 56G 2S2, Can.
SO Biochemistry and Cell Biology (1996), 74(2), 133-154
CODEN: BCBIEQ; ISSN: 0829-8211
PB National Research Council of Canada
DT Journal; General Review
LA English
AB A review and discussion with >100 refs. The two-stranded α-helical coiled-coil is a universal dimerization **domain** used by nature in a diverse group of proteins. The simplicity of the coiled-coil structure makes it an ideal model system to use in understanding the fundamentals of protein folding and stability and in testing the principles of de novo design. The issues that must be addressed in the de novo design of coiled-coils for use in research and medical applications are (i) controlling parallel vs. antiparallel orientation of the polypeptide chains, (ii) controlling the number of helical strands in the assembly (iii) maximizing stability of homodimers or heterodimers in the shortest possible chain length that may require the engineering of covalent constraints, and (i.v.) the ability to have selective heterodimerization without homodimerization, which requires a balancing of selectivity vs. affinity of the dimerization strands. Examples of our initial inroads in using this de novo design motif in various applications include: heterodimer technol. for the detection and purification of recombinant peptides and proteins; a universal dimerization **domain** for biosensors; a two-stage targeting and delivery system; and coiled-coils as templates for combinatorial helical libraries for basic research and drug discovery and as synthetic carrier mols. The universality of this dimerization motif in nature suggests an endless number of possibilities for its use in de novo design, limited only by the creativity of peptide-protein engineers.

L7 ANSWER 261 OF 334 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:161709 CAPLUS
DN 124:317843
TI Economy in **Protein Design**: Evolution of a Metal-Independent ββα Motif Based on the Zinc Finger **Domains**
AU Struthers, Mary D.; Cheng, Richard P.; Imperiali, Barbara
CS Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA, 91125, USA
SO Journal of the American Chemical Society (1996), 118(13), 3073-81
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal

LA English
AB An iterative design process involving the synthesis and structural analyses of five polypeptides patterned after the zinc finger **domains** is described. This process has led to the development of a metal-independent 23-reside folded ββα peptide amide BBA1. In contrast to the zinc fingers and other naturally occurring peptides of similar size, this small monomeric structure folds without the assistance of metal cation ligation or disulfide bridges. To probe the effect of metal binding on the secondary and tertiary structure of peptides throughout the design process, a non-standard amino acid 3-(1,10-phenanthrol-2-yl)-L-alanine (Fen) was incorporated and its unique chromophore utilized for CD anal. Advanced designs were analyzed by both CD and 2-dimensional NMR. The solution structure of BBA1 was determined using NOE restrained simulated annealing. The average RMSD for the backbone atoms of residues 1-22 is 0.9 ± 0.3 Å. Anal. of the resulting structure reveals that the α-helix and β-hairpin are associated via a well-defined hydrophobic core including several key hydrophobic residues. A key design feature of BBA1 is the utilization of a type II' reverse turn to promote β-hairpin formation; a control peptide, in which the β-turn of BBA1 was changed from a type II' to a type II, lacks tertiary structure. Thus the effects of the turn type on the three-dimensional structure of this motif are dramatic. Thus, BBA1 defines a new lower limit for the size of an independently folded polypeptide with native structure.

L7 ANSWER 263 OF 334 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:55036 CAPLUS
DN 124:114969
TI Coupling **protein design** and in vitro selection strategies: improving specificity and affinity of a designed β-protein IL-6 antagonist
AU Martin, Franck; Toniatti, Carlo; Salvati, Anna Laura; Ciliberto, Gennaro; Cortese, Riccardo; Sollazzo, Maurizio
CS Dep. Biotechnology, IRBM, Pomezia, 00040, Italy
SO Journal of Molecular Biology (1996), 255(1), 86-97
CODEN: JMOBAK; ISSN: 0022-2836
PB Academic
DT Journal
LA English
AB The minibody is a designed small β-protein conceived to enable the construction of large libraries of minimal discontinuous epitopes displayed on the surface of filamentous phage. The 61 residue mol. consists of three strands from each of the two β-sheets of the variable **domain** of Igs packed face to face, along with the exposed H1 and H2 hypervariable regions. The authors have previously shown that from a minibody repertoire of more than 50 million mols. displayed on phage, the authors were able to select a minibody with micromolar affinity for human interleukin-6 that behaves as a selective cytokine antagonist. The minibody exposes a surface composed of two constrained loops, which provides the possibility of improving IL-6 binding and specificity by swapping the hypervariable regions, followed by further selection. The authors established exptl. conditions for "stringent" selection such as monovalent phage display, competitive selection and epitope masking. Here the authors show that by virtue of the optimization/selection process, the authors have isolated a minibody with improved antagonist potency and greater specificity. Furthermore, using hIL-6 mutants carrying amino acid substitutions in distinct surface sites it was possible to carefully define the cytokine region that binds the minibody.

L7 ANSWER 266 OF 334 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:937685 CAPLUS
DN 123:333211

TI Guidelines for **protein design**: the energetics of β sheet side chain interactions
AU Smith, Catherine K.; Regan, Lynne
CS Department Molecular Biophysics Biochemistry, Yale University, New Haven, CT, 06520, USA
SO Science (Washington, D. C.) (1995), 270(5238), 980-2
CODEN: SCIEAS; ISSN: 0036-8075
PB American Association for the Advancement of Science
DT Journal
LA English
AB To determine the interaction energy between cross-strand pairs of side chains on an antiparallel β sheet, pairwise amino acid substitutions were made on the solvent-exposed face of the B1 **domain** of streptococcal protein G. The measured interaction energies were substantial (1.8 kcal per mol) and comparable to the magnitude of the β sheet propensities. The exptl. results paralleled the statistical frequency with which the residue pairs are found in β sheets of known structure.

L7 ANSWER 268 OF 334 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:734187 CAPLUS
DN 123:136043
TI New strategies in **protein design**
AU Desjarlais, John R.; Handel, Tracy M.
CS Univ. California, Berkeley, CA, USA
SO Current Opinion in Biotechnology (1995), 6(4), 460-6
CODEN: CUOBE3; ISSN: 0958-1669
PB Current Biology
DT Journal; General Review
LA English
AB A review, with 52 refs. Initially, it was hoped that very simple rules could be used to design proteins that embody all the characteristics of natural proteins. Indeed, with single-**domain** proteins as targets, it has been possible to design proteins that adopt the desired global fold. Yet, designed proteins with well defined structures and properties that mimic those of natural proteins remain elusive. Recent efforts in **protein design** have been directed toward addressing the basis for non-native characteristics in most **protein designs**. Although it is clear that specific tertiary interactions between all residues in a protein contribute to the final folded state, much attention has been placed on optimizing the packing of side chains in the hydrophobic core, with substantial success.

L7 ANSWER 269 OF 334 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:727870 CAPLUS
DN 123:136387
TI Inverse of **protein** folding, the computerized **de novo** design of a **protein** motif
AU Henneke, C. M.
CS AFRC Institute Food Research, UK
SO Protein Engineering Proceedings (1993), Meeting Date 1992, 161-77.
Editor(s): Goodenough, Peter. Publisher: CPL Press, Newbury, UK.
CODEN: 61QIAH
DT Conference
LA English
AB A perfect Greek key jellyroll designer algorithm has been created. The program generates amino acid sequences that are compatible with an 8-stranded perfect Greek key jellyroll protein motif. Each observed property of β-strands, β-sheets, anti-parallel β-barrels, and connecting loops and turns is used to help constrain the designed sequence into its specific 3-dimensional shape. All hydrogen bonds present in the theor. originating β-hairpin of the motif stay in register as the whole 8-stranded **domain** folds at once in an anticlockwise swirl. The amino acid residue for each primary position is selected using

statistical data derived from the protein data bank, and the amino acid composition of known Greek key motifs is employed. The motif's loops are designed according to turn type, and the residues of its single β-hairpin turn are chosen to match the twist of the strands. The algorithm makes use of between-strand amino acid pair correlations as well as secondary structure parameters.

L7 ANSWER 277 OF 334 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:228029 CAPLUS
DN 122:27197
TI A quantitative methodology for the **de novo** design of **proteins**
AU Brenner, Steven E.; Berry, Alan
CS Cambridge Cent. Mol. Recognition, Univ. Cambridge, Cambridge, CB2 1QW, UK
SO Protein Science (1994), 3(10), 1871-82
CODEN: PRCIEI; ISSN: 0961-8368
PB Cambridge University Press
DT Journal
LA English
AB The authors developed a general quant. methodol. for designing **proteins de novo**, which automatically produces sequences for any given plausible protein structure. The method incorporates statistical information, a theor. description of protein structure, and motifs described in the literature. A model system embodying a portion of the quant. methodol. has been used to design many protein sequences for the phage 434 Cro and fibronectin type III **domain** folds, as well as several other structures. Residue sequences selected by this prototype share no significant identity with any natural protein. Nonetheless, 3-dimensional models of the designed sequences appear generally plausible. When examined using secondary structure prediction methods and profile anal., the designed sequences generally score considerably better than the natural ones. The designed sequences are also in reasonable agreement with a sequence template. This quant. methodol. is likely to be capable of successfully designing new proteins and yielding fundamental insights about the determinants of protein structure.

L7 ANSWER 279 OF 334 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:18729 CAPLUS
DN 122:74643
TI Building protein structure and function from modular units
AU Campbell, Iain D.; Downing, A. Kristina
CS Dep. Biochem., Univ. Oxford, Oxford, OX1 3QU, UK
SO Trends in Biotechnology (1994), 12(5), 168-72
CODEN: TRBIDM; ISSN: 0167-7799
DT Journal; General Review
LA English
AB A review, with 30 refs. Many proteins in multicellular organisms are made from combinations of several, clearly identifiable, autonomously folding **domains** or modules. The structures of many of the constituent modules and some module pairs are now known. This review briefly describes some of the recent x-ray crystallog. and NMR structural work on modules 'dissected' from proteins that are often large, membrane-bound and glycosylated. These include important proteins involved in cell adhesion, clotting, fibrinolysis and signaling. The structure and function of the intact proteins is discussed in the light of the recent structural work.

L7 ANSWER 282 OF 334 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:602769 CAPLUS
DN 121:202769
TI Total chemical synthesis, characterization and immunological properties of a MHC class I model using the TASP concept for **protein de novo** design
AU Tuchscherer, G.; Servis, C.; Corradin, G.; Blum, U.; Rivier, J.; Mutter,

M.
CS Salk Inst., La Jolla, CA, 92037, USA
SO Pept. 1992, Proc. Eur. Pept. Symp., 22nd (1993), Meeting Date 1992, 848-9. Editor(s): Schneider, Conrad H.; Eberle, Alex N. Publisher: ESCOM, Leiden, Neth.
CODEN: 60LUAN
DT Conference
LA English
AB The authors have recently focused on the design of TASP mols. of 4α-helix bundle topol., in which antigenic helical segments of protein surface **domains** are assembled on suitable templates. Here, in a first approach, the native sequence 58-74 of the α1 heavy chain **domain** of HLA-A2 was modeled in order to increase helix stability and amphiphilicity of the 17-mer peptide, preserving the residues for pot. T-cell receptor binding properties.

L7 ANSWER 296 OF 334 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1993:189468 CAPLUS
DN 118:189468
TI Total chemical synthesis, characterization, and immunological properties of an MHC class I model using the TASP concept for **protein de novo** design
AU Tuchscherer, G.; Servis, C.; Corradin, G.; Blum, U.; Rivier, J.; Mutter, M.
CS Salk Inst., La Jolla, CA, 92037, USA
SO Protein Science (1992), 1(10), 1377-86
CODEN: PRCIEI; ISSN: 0961-8368
DT Journal
LA English
AB The design, total chemical synthesis, and immunol. properties of a 4-α-helix bundle template-assembled synthetic protein (TASP) mimicking some of the structural features of the major histocompatibility complex (MHC) class I is described. In a 1st approach, the native sequence 58-74 of the α1 heavy chain **domain** of HLA-A2 was modeled to increase helix stability and amphiphilicity of the 17-mer peptide, preserving the residues for potential T-cell receptor (TcR) binding properties. According to the TASP concept, these helical segments were covalently attached to a cyclic template mol. designed for the induction of a 4-helix-bundle topol. of the assembled peptide blocks. After extensive HPLC purification, stepwise solid-phase synthesis resulted in a TASP mol. of high chemical purity as demonstrated by anal. HPLC, mass spectrometry, and amino acid anal. CD spectroscopic investigations are consistent with the onset of a partial α-helical conformation in aqueous buffer as well as in TFE. Antibodies raised directly against this 4-α-helix bundle TASP mol. (without prior conjugation to a carrier mol.) were detected by ELISA. Flow cytometry studies showed that these antibodies recognize the native MHC class I mol. on the surface of HLA-A2-pos. cells. Thus, the TASP approach represents a versatile tool for mimicking conformational epitopes.

L7 ANSWER 299 OF 334 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1992:607448 CAPLUS
DN 117:207448
TI Zinc finger-DNA recognition: analysis of base specificity by site-directed mutagenesis
AU Nardelli, Jeannette; Gibson, Toby; Charnay, Patrick
CS Lab. Genet. Mol., Ec. Norm. Super., Paris, F-75230, Fr.
SO Nucleic Acids Research (1992), 20(16), 4137-44
CODEN: NARHAD; ISSN: 0305-1048
DT Journal
LA English
AB Zinc fingers of the Cys2/His2 class are conserved 28-30 amino acid motifs that constitute an important and widespread family of eukaryotic DNA-binding **domains**. It is therefore of great interest to

understand the rules that govern specific recognition of DNA by zinc fingers. The DNA-binding **domain** of the transcription factor Krox-20 consists of three zinc fingers, each of them making its primary contacts with a three-base pair subsite. A data base-guided site-directed mutagenesis anal. of Krox-20 was performed: nine derivs. were generated, in which one to three amino acid changes had been introduced within finger 2, at positions which were likely to affect the specificity of DNA recognition. The affinities of the different proteins for a panel of potential DNA binding sites were estimated by gel retardation assay. Six of the derivs. bound specific targets with affinities comparable to that of wild type Krox-20 for its consensus binding site. However, the specificity of recognition was dramatically modified at the expected bases, in a manner that could be explained by examining the newly introduced amino acids within the context of the overall finger/triplet interaction. These data provide new insights into the details of zinc finger-DNA interactions and, combined with the modular nature of zinc fingers, illustrate both the potential and the difficulties of utilizing these motifs for designing DNA-binding proteins with novel specificities.

L7 ANSWER 302 OF 334 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1992:485882 CAPLUS
DN 117:85882
TI Computer-aided **protein design**: three-dimensional model building of the saruplase structure
AU Strassburger, W.; Winter, W.; Steffens, G. J.; Guenzler, W. A.; Flohe, L.
CS Cent. Res., Gruenenthal GmbH, Aachen, W-5100, Germany
SO Supercomput. Chem. 2, Debis Workshop (1991), Meeting Date 1990, 159-66. Editor(s): Harms, Uwe. Publisher: Springer, Berlin, Germany. CODEN: 58AVAE
DT Conference
LA English
AB Modeling studies of the three-dimensional structures of the saruplase **domains** are presented. The model of the N-terminal EGF-like **domain** highlights amino acids residues which might be involved in interactions with saruplase specific receptors. The distribution of charged residues on the surface of the kringle model is different from other kringle structures. The model structure of the catalytic serine protease **domain** points to surface loops, which surround the active site and may participate in interactions with plasminogen. Starting from the structures of the isolated **domains** a model for the entire enzyme is constructed which is compatible with exptl. results.

L7 ANSWER 305 OF 334 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1992:251577 CAPLUS
DN 116:251577
TI **Protein design** on computers. Five new proteins: Shpilka, Grendel, Fingerclasp, Leather, and Aida
AU Sander, Chris; Vriend, Gerrit; Bazan, Fernando; Horovitz, Amnon; Nakamura, Haruki; Ribas, Luis; Finkelstein, Alexei V.; Lockhart, Andrew; Merkl, Rainer; et al.
CS Eur. Mol. Biol. Lab., Heidelberg, D-6900, Germany
SO Proteins: Structure, Function, and Genetics (1992), 12(2), 105-10 CODEN: PSFGEY; ISSN: 0887-3585
DT Journal
LA English
AB The authors tested available design tools and explored new design strategies to design proteins. Five novel proteins were designed: Shpilka, a sandwich of 2 4-stranded β-sheets, a scaffold on which to explore variations in loop topol.; Grendel, a 4-helical membrane anchor, ready for fusion to water-soluble functional **domains**; Fingerclasp, a dimer of interdigitating β-β-α units, the simplest variant of the handshake structural class; Aida, an antibody binding surface intended to be specific for flavodoxin; Leather, a minimal NAD binding **domain**, extracted from a larger protein. Each design is

available as a set of 3-dimensional coordinates, the corresponding amino acid sequence and a set of anal. results. The designs are placed in the public **domain** for scrutiny, improvement, and possible exptl. verification.

L7 ANSWER 308 OF 334 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1991:649025 CAPLUS
DN 115:249025
TI New molecular biology methods for protein engineering
AU Zoller, Mark J.
CS Dep. Protein Eng., Genentech, South San Francisco, CA, 94080, USA
SO Current Opinion in Structural Biology (1991), 1(4), 605-10
CODEN: COSBEF; ISSN: 0959-440X
DT Journal; General Review
LA English
AB A review with 41 refs. Recent advances in the application of mol. biol. techniques to the study of protein structure and function are discussed. Methods for oligonucleotide-directed mutagenesis; mutational strategies for identifying functional residues and **domains**; systems for expression; and, future developments are explored. Few new methods were reported in 1990; however, a number of the papers represent refinements of previously reported strategies.